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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/487,841	01/19/00	ROZEN R	50004/003004

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EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/487,841	Applicant(s) ROZEN ET AL.	
	Examin r Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *12,15 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,14,and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

This application claims the benefit of provisional application 60/071,622 filed 1-16-98 and is a continuation-in part of 09/371,341 filed 8-10-99 which is a continuation-in-part of 09/232,028 filed 1-15-99, abandoned 8-25-00.

The preliminary amendment filed 12-11-00 has been entered. Claim 1 has been amended. Claims 1-21 are pending. Claims 1-11, 13, 14 and 21 are under consideration.

1. Applicant's election without traverse of group I, claims 1-11, 13, 14 and 21, in Paper No. 7 is acknowledged.

2. Claims 12 and 15-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: how to inhibit or activate methionine synthase

reductase biological activity and whether the inhibition or activation of methionine synthase reductase biological activity could treat or prevent cancer, cardiovascular disease, Down's syndrome, or neural tube defects in a subject.

5. Claims 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "claim D" in claim 4 line 8 is vague and renders the claim indefinite. It is unclear what "claim D" means and which preceding claim is intended.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-11, 13, 14 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increased risk for mothers to develop neural tube defects (NTD) with combination of homozygous mutant MTRR genotype having an A/G polymorphism at bp 66, which yields an isoleucine (22I) or a methionine (22M) at amino acid position 22, and low cobalamin; mothers of Down's Syndrome babies are more likely to have MTRR polymorphism of A->G at nucleotide position 66 and methylenetetrahydrofolate reductase (MTHFR) polymorphism C->T at nucleotide position 677 than control mothers; individuals

having a MTRR homozygous 66 A->G polymorphism are at greatest risk of developing coronary artery disease (CAD) and the association of the MTRR genotype with CAD is not modulated by vitamin B12 status or MTHFR genotype (See specification page 56, 58, 63, 66, 68), and the association of homocysteine, folic acid, vitamin B6 and vitamin B12 with cancer and vascular disease as disclosed by Mayer et al., 1996 (JACC, Vol. 27, No. 3, p. 517-527), does not reasonably provide enablement for a method of treating or preventing cancer, cardiovascular disease, Down's Syndrome, or NTD in a subject by inhibiting or activating MTRR biological activity, a method of treating or preventing cardiovascular disease or Down's syndrome by using metabolite or cofactor, such as folate, cobalamin, s-adenosyl methionine, betaine or methionine with or without detecting an increased risk of developing cancer, cardiovascular disease, NTD or Down's syndrome in a test subject, and a method for detecting an increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease in any mammalian fetus or embryo by detecting any heterozygous or homozygous MTRR polymorphism in either or both future parents of said embryo or fetus, or in said embryo or fetus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-5 are directed to a method of treating or preventing cancer, cardiovascular disease, Down's Syndrome, or NTD in a subject by inhibiting or activating MTRR biological activity, and a method of treating or preventing cancer, cardiovascular disease, NTD or Down's Syndrome by using metabolite or cofactor, such as folate, cobalamin, s-adenosyl methionine,

betaine or methionine with or without detecting an increased risk of developing cancer, cardiovascular disease, NTD or Down's Syndrome in a test subject. Claims 6-11, 13, 14 and 21 are directed to a method for detecting an increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease in any mammalian fetus or embryo by detecting any heterozygous or homozygous MTRR polymorphism in either or both future parents of said embryo or fetus, or in said embryo or fetus. Claim 21 specifies the cardiovascular disease is a premature coronary artery disease.

The specification of the present application discloses increased risk for mothers to develop neural tube defects (NTD) with combination of homozygous mutant MTRR genotype having an A/G polymorphism at bp 66, which yields an isoleucine (22I) or a methionine (22M) respectively at amino acid position 22, and low cobalamin; mothers of Down's syndrome babies are more likely to have MTRR polymorphism of A->G at nucleotide position 66 and methylenetetrahydrofolate reductase (MTHFR) polymorphism C->T at nucleotide position 677 than control mothers; and individuals having a MTRR homozygous 66 A->G polymorphism are at greatest risk of developing coronary artery disease (CAD) and the association of the MTRR genotype with CAD is not modulated by vitamin B12 status or MTHFR genotype (See specification page 56, 58, 63, 66, 68). The claims encompass using any agent that inhibits or activates the MTRR biological activity to treat or prevent cancer, cardiovascular disease, NTD or Down's Syndrome in a subject and detecting an increased risk of developing the disease set forth above by detecting any heterozygous or homozygous MTRR polymorphism.

The specification of the present application fails to provide adequate guidance and evidence for the correlation between the inhibition or activation of MTRR biological activity and treating or preventing cancer, cardiovascular disease, NTD or Down's Syndrome in a subject. The specification also fails to teach how to use the agent that inhibits or activates MTRR biological activity to treat or prevent the diseases set forth above. The agent that inhibits or activates MTRR biological activity could be a nucleic acid, a protein, an antibody or other organic compounds. The specification fails to teach where and how to administer those agents to a subject, the dose required to provide therapeutic effects, and whether sufficient agent would be present for a sufficient duration of time at the targeted site to provide therapeutic effect in a subject *in vitro* or *in vivo* to treat or prevent the diseases set forth above. In view of such, one skilled in the art would not know which agent is to be used and how to use said agent to treat or prevent the diseases set forth above.

The claims read on gene therapy, and the state of the prior art was not well developed and was highly unpredictable at the time of the invention. Verma et al. (Sept. 1997, Nature, Vol. 389, pages 239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, McGraw-Hill, New York, 1996, p. 77-101) indicates that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo*

consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy *in vivo*. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e.g. bridging pages 81-82). Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (page 239, col. 3). Similarly, the administration route of a composition containing a protein to a subject, the sufficient amount of the protein present in the targeted site, the stability of the protein at the targeted site, and the protein's compartmentalization within the cell are all important factors for a successful protein therapy.

Further, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages

53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

The specification fails to provide adequate guidance and evidence for treating or preventing cancer, cardiovascular disease, NTD or Down's Syndrome by using metabolite or cofactor, such as folate, cobalamin, s-adenosyl methionine, betaine or methionine. The specification fails to teach where and how to administer those metabolite or cofactors to a subject, the dose required to provide therapeutic effects, and whether sufficient metabolite or

cofactors would be present for a sufficient duration of time at the targeted site to provide therapeutic effect in a subject *in vitro* or *in vivo* to treat or prevent the diseases set forth above. Mayer et al., 1996 (JACC, Vol. 27, No. 3, p. 517-527) teaches elevated levels of homocysteine in cancer patients and higher plasma homocysteine levels in patients with vascular disease than a normal subject (e.g. p. 520, 522), and folic acid alone, or combined with vitamins B12 and B6, or the combination of B12 or B6 could reduce the homocysteine concentrations. However, vitamin B12 alone would not be expected to reduce homocysteine unless there is suboptimal B12 status or frank B12 deficiency, and administration of vitamin B6 alone in normal subject does not lower fasting plasma homocysteine concentration (e.g. p. 523). Therefore, it is unclear and unpredictable whether any of the metabolite or cofactor alone or even combined would be able to provide therapeutic effects in a subject for the treatment or prevention of the disease set forth above. In view of such, one skilled in the art would require undue experimentation to practice over the full scope of the invention claimed.

The specification fails to provide adequate guidance and evidences for any polymorphism or mutation within the MTRR gene other than the polymorphism disclosed in the specification and fails to teach the correlation of said polymorphism or mutation with increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease in any mammalian fetus or embryo. It was known in the art that different polymorphism or mutation within a gene could result in dramatic different effect on the function of the gene product and therefore, different correlations with increased risk of developing a NTD, Down's Syndrome, or cardiovascular

disease. Further, the specification of the present application discloses that no increased risk of developing NTD could be correlated to a mother or child having homozygous MTRR 22M polymorphism (specification, bridging p. 57-58) and no correlation of increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease with heterozygous or homozygous MTRR G/A polymorphism at nucleotide position 110, or with heterozygous MTRR 22IM polymorphism has been disclosed. It was unclear and unpredictable at the time of the invention whether a polymorphism or a mutation within MTRR gene either heterozygous or homozygous would be correlated to increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease, and one skilled in the art at the time of the invention would not be able to predict whether a test subject would have increased risk of developing said diseases by detecting any heterozygous or homozygous polymorphism or mutation within MTRR gene in a test subject.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 2 and 5 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Mayer et al., 1996 (JACC, Vol. 27, No. 3, p. 517-527).

Claims 2 and 5 are directed to a method of treating or preventing cardiovascular disease or Down's Syndrome by administering therapeutically effective dose of a metabolite or cofactor, such as folate, cobalamin, s-adenosyl methionine, betaine or methionine, to a subject. Claim 5 specifies the cardiovascular disease is premature coronary artery disease.

Mayer teaches elevated levels of homocysteine in cancer patients and higher plasma homocysteine levels in patients with vascular disease than a normal subject (e.g. p. 520, 522). Mayer also teaches that folic acid alone, or combined with vitamins B12 (cobalamin) and B6, or the combination of B12 or B6 could reduce the homocysteine concentrations in patients with coronary atherosclerosis (e.g. p. 523). Thus, claims 2 and 5 are clearly anticipated by Mayer.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

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